Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 91-108 are pending in the application, with claims 91 and 100 being the independent claims. Claims 1-90 are cancelled without prejudice to or disclaimer of the subject matter therein. Claims 91, 95, 96, 100, 104 and 105 are sought to be amended. Support for the amendment to claims 91 and 100 adding the recitation "comprising rhodamine" can be found, for example, in the specification at page 12, lines 4-5. Support for the amendment to claims 95 and 104 adding the recitation "wherein Z is benzyoxycarbonyl" can found in previously presented claims 98 and 107, and in the specification at page 66, lines 18-27. Support for the amendment to claims 96 and 105 adding definitions for R_4 and R_5 can be found, for example, in Applicants' specification at page 16, line 17. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 91-108 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Landrum *et al.*, US 5,976,822. (Office Action, page 2). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that "Landrum (5,976,822) entitled 'Method and Reagent for Monitoring Apoptosis and Distinguishing Apotosis from Necrosis' teaches a

blocked caspase substrate where y is rhodamine, R1 is Cbz and (AA)n is a residue of an amino acid DEVD." (Office Action, page 2).

Applicants respectfully disagree. Claims 91 and 100 (and their respective dependent claims) are directed to a reporter compound of formulae II or V having a *N*-terminal protecting group at R_1. In contrast to the present invention which uses a reporter compound having a protecting group, Landrum *et al.* describes a methodology which uses an assay reagent "having an *unblocked* leaving group selected for cleavage by an enzyme . . . ." Landrum *et al.*, column 3, lines 12-29 (emphasis added). Removal of the blocking (or protecting) group is critical to the methodology described by Landrum *et al.*:

> The blocking group which is blocking (protecting) the leaving group is then removed from the reaction product to obtain an assay compound ("intermediate compound" is formed at this step if the final assay compound is a salt) which contains an indicator group and a leaving group. The reactions are conducted to obtain a free amino acid xanthine derivative by methods known to those skilled in the art. When the blocking group on the indicator group comprises benzyloxycarbonyl (CBZ), the blocking group is removed by a catalytic reaction of the reaction product in an organic solvent with hydrogen in the presence of palladium or platinum. When the blocking group on the indicator group comprises 9-fluorenylmethyloxycarbonyl (FMOC), the blocking group is typically removed by the reaction of the reaction product in a polar solvent with an organic base. Further details of this process are shown in Example 1.
>
> To confirm that the blocking group has been removed and the resulting intermediate compound has formed, the intermediate compound is analyzed by analytical reverse phase HPLC. In addition, the resulting intermediate compound can be further confirmed by developing a thin layer chromatography plate in an organic solvent.

Landrum *et al.*, column 8, lines 9-30.

Indeed, both of Landrum *et al.*'s independent claims are directed to a composition or methodology comprising an "assay compound having an unblocked leaving group." Landrum *et al.*, claims 1 and 10.

As indicated by the Examiner, Landrum *et al.* does refer to protected compounds where y is rhodamine, R1 is Cbz and (AA)n is a residue of an amino acid DEVD. *See* Landrum *et al.*, column 2, lines 50-53. Based on the excerpted passages above, however, such protected compounds are not useful in the methodologies described and claimed by Landrum *et al.* Moreover, Landrum *et al.* teaches away from using such protected compounds:

> . . . the reagent should contain an unblocked assay compound which has a reaction rate which is at least 2 times, preferably at least 5 times, more preferably at least 100 times, most preferably at least 1000 times the reaction rate of a corresponding blocked assay compound. For example, the unblocked assay compounds of the present invention which contain unblocked amino and or peptide leaving groups have an enzymatic reaction rate which is considerably greater than the reaction rate of the corresponding compound wherein the amine group(s) on the leaving group is blocked by, for example, a Cbz group.

Landrum *et al.*, column 12, lines 21-32.

One skilled in the art would not be motivated to alter the methodologies described by Landrum *et al.* by replacing an assay reagent comprising an unblocked leaving group with an assay reagent comprising a blocked leaving group.

Because Landrum *et al.* does not render obvious Applicants' claimed methodologies, it is respectfully requested that the rejection of claims 91-108 under 35 U.S.C. § 103(a) be withdrawn.

Rejections under 35 U.S.C. § 112

Claims 91-108 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner is of the opinion that "[t]he claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in that art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." (Office Action, page 3). Applicants respectfully traverse this rejection.

In regard to claim 91 (and presumably claim 100), the Examiner is of the opinion "the term 'y is a fluorogenic or fluorescent moiety' lacks enablement as it would require one of ordinary skill in this art undue experimentation to determine which would work in the instant invention. The specification as originally filed shows Y is rhodamine 110 only as claimed in present claim 94." (Office Action, page 3).

Applicants respectfully disagree. However, solely to expedite prosecution and not in acquiescence to the rejection, Applicants have amended claims 91 and 100 to specify that y is a fluorogenic or fluorescent moiety comprising rhodamine.

Further in regard to claim 91 (and presumably claim 100), the Examiner is of the opinion that "for the case where n is zero thereby Asp is the only amino acid, claim 91 does not correspond with the description of the invention wherein an amide bond between two amino acids must be cleavable." (Office Action, page 3).

Applicants respectfully disagree. Referring to the *Summary of the Invention* on page 11 starting on line 10:

> The invention relates to fluorogenic or fluorescent reporter compounds of formula I:

x-y-z (I)

or biologically acceptable salts or pro-reporter molecules (such as methyl ester form of carbonyl-containing amino acid residues) thereof, wherein x and z is the same or different and is a peptide or amino acid or acyl group or other structure such that the compounds of Formula I is a substrate for caspases, or a substrate for other proteases or peptidases or other enzymes; and wherein the scissile bond is only one or both of the x-y and y-z bonds in Formula I when x is the same as z, or wherein the scissile bond is only one of the x-y or y-z bond in Formula I when x is not the same as z. y is a fluorogenic or fluorescent moiety.

Preferred compounds are represented by the Formula II:

R_1-$(AA)_n$-Asp-y-Asp-$(AA)_n$-R_1 (II

Specification, page 11, lines 12-25.

When n is zero in Formula II, Applicants describe bond cleavage between one or both R_1-Asp groups (representative of "x" and/or "z" in formula I) and the fluorogenic or fluorescent moiety y that is released in response to enzymatic activity. Likewise, when n is zero in formula V, Applicants describe bond cleavage between the R_1-Asp group and the fluorogenic or fluorescent moiety y is released in response to enzymatic activity. Thus, one skilled in the art would recognize amide bond cleavage between two amino acids is not required, but rather amide bond cleavage between the Asp amino acid residue and the fluorogenic or fluorescent moiety y is also possible.

Applicants respectfully request that the Examiner reconsider and withdraw the rejections under rejection under 35 U.S.C. § 112, first paragraph.

Claims 91-108 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point our and distinctly claim the subject

matter which application regards as the invention. (Office Action, page 4). Applicants respectfully traverse this rejection.

In regard to claim 91, the Examiner is under the opinion that "[c]laim 91 is a method claim where the second step is recording a result but no determining of fluorescence is claimed." (Office Action, page 5).

Applicants respectfully disagree. Determining of fluorescence is required by the claim as one must determine the fluorescence of cancer or control cells before one can record the fluorescence. Methods to determine a fluorescent signal, including use of a spectrophotometer, spectrofluorometer or fluorometric microtiter plate, are provided in the Applicants' written description (Examples 72-84, pages 115-127). Thus, the metes and bounds of these claims are clear.

In regard to claim 91(a), the Examiner is under the opinion that the invention would not work if n is zero. (Office Action, page 5).

Applicants respectfully disagree. As discussed above, amide bond cleavage between an Asp amino acid residue and a fluorogenic or fluorescent moiety y will occur in response to enzymatic activity. Therefore, the invention works if n is zero.

In regard to claim 92, the Examiner is of the opinion that the invention would not work if r is zero. (Office Action, page 5).

Applicants respectfully disagree. When r is zero, the recited blocking group R_6 would be $CH_3(OCH_2CH_2)_sOCO$- wherein s is 1-4. One skilled in the art would recognize alkoxyalkylcarbamates (e.g.; methoxyethyl carbamate when s is 1) are common blocking groups. Therefore, the invention works if r is 0.

In regard to claims 95 and 104, the Examiner is of the opinion that "the term 'Z' is not defined." (Office Action, page 5). Applicants herewith amend claims 95 and 104 to include a definition for the term Z.

In regard to claim 105, the Examiner is of the opinion that "R4, R5 and R6 are not defined." (Office Action, page 5).

Applicants respectfully disagree. The term R_6 is defined in claim 100 as "a blocking group which is not an amino acid or a derivative of an amino acid." Claim 105 depends from claim 100. Accordingly, R_6 as used in the present invention is defined. Solely to expedite prosecution and not in acquiescence to the rejection, Applicants herewith amend claims 96 and 105 such that R_4 and R_5 are defined.

Applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. § 112, second paragraph.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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